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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/720,840	09/05/2001	Peter Francis Leadlay	0380-P02382U	6757

110 7590 06/17/2005

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EXAMINER	
KERR, KATHLEEN M	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 06/17/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/720,840	LEADLAY ET AL.	
	Examiner	Art Unit	
	Kathleen M. Kerr	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 March 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *54-66,68,70,71,73 and 75* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *64* is/are allowed.

6)☒ Claim(s) *54-59,63,70,71,73 and 75* is/are rejected.

7)☒ Claim(s) *60-62,65,66 and 68* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10 September 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Application Status

1. A request for continued examination under 37 C.F.R. § 1.114, including the fee set forth in 37 C.F.R. § 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 C.F.R. § 1.114, and the fee set forth in 37 C.F.R. § 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 C.F.R. § 1.114. Applicant's submission filed on February 25, 2005 has been entered.

2. In response to the previous Office action, a Final rejection (mailed on September 21, 2004), Applicants filed a response and amendment received on February 25, 2005 and an RCE on March 24, 2005 entering said amendment. Said amendment cancelled Claims 67, 69, 72, 74, and 76 and amended Claims 54, 60, 63, 64, 70, 73, and 75. Thus, Claims 54-66, 68, 70, 71, 73, and 75 are pending in the instant Office action and will be examined herein.

Priority

3. As previously noted, the instant application is granted the benefit of priority for International Application No. PCT/GB99/02044 filed on June 29, 1999 and UK Application No. 9814066.4 filed on June 29, 1998.

New - Claim Objections

4. Claims 65, 66, and 68 are objected to for improperly referring to an antecedent in the previous claim. The phrase "wherein (AT)" must be replaced with ---wherein said AT---.

Withdrawn - Claim Rejections - 35 U.S.C. § 112, second paragraph

5. Previous rejection of Claims 54-63 under 35 U.S.C. § 112, second paragraph, as being indefinite for the nature of the loading module in the phrase "at least the first of said extension modules is not naturally associated with said loading module" is withdrawn by virtue of Applicant's cancellation of said language from the instant claims.

6. Previous rejection of Claim 63 under 35 U.S.C. § 112, second paragraph, as being indefinite for the phrase "wherein the starter unit is derived from a loading domain" is withdrawn by virtue of Applicant's amendment.

7. Previous rejection of Claims 73-76 under 35 U.S.C. § 112, second paragraph, as being indefinite is withdrawn by virtue of Applicant's amendment and/or cancellation of said claims.

New - Claim Rejections - 35 U.S.C. § 112, second paragraph

8. Claim 56 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In Claim 56, the phrase "natural extension module" is unclear as to its metes and bounds. For example, allelic variants would be considered within the metes and bounds of the claims while genetically engineered point mutations would not. Since the metes and bounds of *all* naturally occurring allelic variants are unknown, what is made via genetic engineering today (outside the scope of the claim) may be found as a naturally occurring allelic variant tomorrow (inside the scope of the claim). Moreover, no difference between extension module AT domains and loading module AT domains is described except for the KSq, which is already a limitation of the instant claim. Thus, the metes and bounds are ill defined. Clarification is required.

9. Claim 57 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase "produced by mutation" renders the antecedent basis from Claim 54 unclear since no mutation is mentioned in Claim 54. Moreover, the scope of the claim is difficult to understand in the absence by virtue of the product-by-process language of Claim 54". Clarification is required.

Withdrawn - Claim Rejections - 35 U.S.C. § 112, first paragraph

10. Previous rejection of Claims 64 and 67 under 35 U.S.C. § 112, first paragraph, new matter, is withdrawn by virtue of Applicant's amendment limiting the instant claims to that which is supported on page 27 of the specification as originally filed.

11. Previous rejection of Claim 72 under 35 U.S.C. § 112, first paragraph, new matter, is withdrawn by virtue of Applicant's cancellation of said claim.

12. Previous rejection of Claim 75 under 35 U.S.C. § 112, first paragraph, new matter, is withdrawn by virtue of the Examiner's reconsideration in view of Applicant's arguments. Indeed, on pages 21-22 of the specification, the loading module of tylosin is envisioned with a plurality of extension modules to produce 12, 14, or 16-membered macrolides. Moreover, it is not considered new matter to merely exclude the option of 16-membered macrolides.

13. Previous rejection of Claims 54-63 under 35 U.S.C. § 112, first paragraph, written description, as previously presented, is withdrawn by virtue of Applicant's amendment and arguments.

> Moreover, the Examiner notes that previously the record details:
>
> "By the word "engineered", the instant claims exclude KSq domains that naturally occur, such as that of tylosin, which is used in a hybrid PKS taught by Kuhstoss *et al.*"

While the Examiner maintains that it is Applicant's intent to exclude naturally-occurring species of KSq domains from the instant claims, this is not accomplished with the instant claim language. Thus, the previous art rejections using Kuhstoss *et al.* are reinstated below.

14. Previous rejection of Claims 60, 64, and 69-71 under 35 U.S.C. § 112, first paragraph, written description, for the genus of hybrid PKSs comprising an AT5 from a monensin PKS gene cluster is withdrawn by virtue of Applicant's cancellation of this subject matter from the instant claims.

15. Previous rejection of Claim 71 under 35 U.S.C. § 112, first paragraph, written description, for the genus of hybrid PKSs comprising the extension modules of immunomycin (FK-520) PKS is withdrawn by virtue of Applicant's amendment removing this limitation from the claims.

16. Previous rejection of Claims 70, 72 and 74 under 35 U.S.C. § 112, first paragraph, written description, for the KSq domain of the oleandomycin PKS gene cluster is withdrawn by virtue of Applicant's arguments pointing out its support in Figure 4.

New or Maintained - Claim Rejections - 35 U.S.C. § 112, first paragraph

17. Previous rejection of Claim 71 under 35 U.S.C. § 112, first paragraph, new matter, is maintained. Applicant's arguments have been fully considered but are not deemed persuasive for

the following reasons. Applicant argues that because Claim 64 has been amended, Claim 71 is fully supported; the Examiner disagrees. While Claims 64 and 65, 66, and 68 are fully supported on page 27 of the specification, linking loading modules having KSq domains, particular AT domains, and ACP domains to extension modules specifically extension modules of erythromycin, rifamycin, avermectin, rapamycin or FK506 PKSs is not supported. While generic use of these PKSs is supported, particular use of their extension modules and/or in combination with AT6 of niddamycin, AT4 of FK506, and AT5 of spiramycin is not.

18. Previous rejection of Claim 70 under 35 U.S.C. § 112, first paragraph, new matter, is maintained. Applicant's arguments have been fully considered but are not deemed persuasive for the following reasons. Applicant argues that Claim 70 as amended is supported in Example 11; the Examiner disagrees. Example 11 supports claims to KSq (KSq of oleandomycin)-AT(AT2 of rapamycin)-ACP(ACP-L of DEBS) wherein the extension modules are DEBS modules 1 and 2 and not wherein the extension modules are from any PKS. Thus, this particular combination as found in Claim 70 is considered new matter.

19. Previous rejection of Claim 73 under 35 U.S.C. § 112, first paragraph, written description, for not having adequate written description for the loading module of monensin is maintained. Applicant's arguments have been fully considered but are not deemed persuasive. Applicant argues that the instant claim is described, particularly in view of in *In re Wallach*, which notes that a partial amino acid sequence and additional characteristics of the protein are adequate to describe the protein. The Examiner disagrees. Firstly, no additional characteristics, such as protein size, are provided for the monensin loading module and the disclosure of only the

KSq and AT didomain is insufficient to describe the entire loading module without additional characteristics. Moreover, the instant claim is drawn to a necessarily *recombinant* protein comprising the monensin loading module. Therefore, the full sequence is crucial to the description inasmuch as encoding DNA is used to produce the claimed invention. For all these reasons, Applicant's arguments are not persuasive and the instant rejection is maintained.

Withdrawn - Claim Rejections - 35 U.S.C. § 103

20. Previous rejection of Claim 76 under 35 U.S.C. § 103(a) as being unpatentable over Kuhstoss *et al.* (see PTO-892 from previous Office action) in view of Khosla *et al.* (USPN 5,672,491) is withdrawn by virtue of Applicant's cancellation of said claim.

New - Claim Rejections - 35 U.S.C. § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

21. Claims 54-57, 59 and 63 are rejected under 35 U.S.C. § 102(b) as being anticipated by Kuhstoss *et al.* The instant claims are drawn to PKSs that produce polyketides (16-membered macrolides from propionate starter units) wherein the loading module of said PKS is methylmalonyl-specific and contains a KSq domain, an AT domain with an arginine at the active site, and an ACP domain.

Kuhstoss *et al.* teach a hybrid polyketide synthase (PKS) comprised of the loading module (KS^Q-AT-ACP) of the tylosin PKS and the first two extension modules of spiramycin

PKS (see page 233, left column and Figure 3). The loading module of the tylosin PKS inherently has the capacity for decarboxylation as itemized in Claim 54. The hybrid PKS produces a 16-membered polyketide (see Figure 3), which production attests to the ability of the loading domain to supply the extension modules with the growing polyketide chain. The loading module of the tylosin PKS contains a KS^Q domain (a ketosynthase domain having a glutamine, not a cysteine, as an active site residue) and the AT domain contains an arginine. The loading module of the tylosin PKS is specific for methylmalonyl-CoA and propionate and includes and acyl carrier protein."

The Examiner notes that the naturally occurring KSq domain of the loading module of the tylosin PKS reads on the "engineered" KSq domain as described in Claim 54 because the product-by-process language does not exclude it. The limitation of being "obtained by replacing the active site cysteine of a KS domain of an extension module" does not require the KSq of the claim to be recombinant since any KSq having the same features as a "replaced" KSq can be considered. Moreover, requiring the KS originally be from an extender KS adds no real limitation since the only disclosed difference between a KS of a loading module and a KS of an extender module is, in fact, the glutamine at the active site.

The Examiner stresses that these are product claims, not method claims, and the product of the art need not be produced by the process in the claim so long as said product can be produced whatsoever. Moreover, while the specification on page 18 indicates that "engineered" is in contrast to "natural" (thus, excluding naturally occurring KSq domains), this limitation cannot be read into the claims. This opinion is set forth after reconsideration of the record by the Examiner.

New - Claim Rejections - 35 U.S.C. § 103

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

22. Claim 58 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Kuhstoss *et al.* The instant claim is drawn to PKSs that produce polyketides (16-membered macrolides from propionate starter units) wherein the loading module of said PKS is malonyl-specific and contains a KSq domain, an AT domain with an arginine at the active site, and an ACP domain.

Kuhstoss *et al.* teach as described above. Kuhstoss *et al.* do not teach using a malonyl-specific KSq, such as that of spiramycin, in a hybrid PKS.

At the time of the invention, it would have been obvious to one of skill in the art to make the claimed invention of a KSq of spiramycin with the first two extender modules of tylosin as the "opposite" experiment as that which was performed. One would have been motivated to produce the claimed invention as a simple proof-of-principle experiment.

23. Claims 73 and 75 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Khosla *et al.* (USPN 5,712,146). The instant claim is drawn to PKSs that has a monensin or tylosin loading module and a plurality of extension modules to produce a 14-membered macrolide (or optionally a 16-membered macrolide for Claim 73) other than a 14-membered macrolide having a 13-methyl group due to incorporation of an unsubstituted acetate starter.

Khosla *et al.* teach the basic construction of type I (modular) PKS enzymes. Type I PKS modules minimally contain a ketosynthase (KS) domain, an acyltransferase (AT) domain, and an acyl carrier protein (ACP) domain (see column 19, lines 12-20). Khosla *et al.* teach hybrid PKS enzymes using a combination of "enzymes, modules, active sites or portions thereof derived from aromatic, modular or fungal PKS gene clusters" (see column 10, lines 40-45). Thus, Khosla *et al.* teach the combination of any of these modules to produce a minimal PKS.

Khosla *et al.* specifically teach that "examples of hybrid replacement clusters include clusters with genes derived from two or more of ... erythromycin ..., tylosin, ...spiramycin, ...[and] monensin ... synthase gene clusters (see column 14, lines 26-34). The polyketides produced by mixing and matching the PKS domains described in Khosla *et al.* minimally mimic those found in the PKS gene clusters described (see column 14, lines 30-33) and include 14- and 16-membered macrolides. For example, the monensin loading module with extension modules of any of erythromycin, tylosin, or spiramycin read on Claim 73; and the tylosin loading module with extension modules of erythromycin read on Claim 75 because the tylosin loading module incorporates propionate (not an acetate) starter unit.

At the time of the invention, it would have been obvious to one of ordinary skill in the art to use the teachings of Khosla *et al.* to produce a hybrid PKS having the monensin loading module and any of erythromycin, tylosin, or spiramycin extension modules to produce a 16-membered macrolide (tylosin or spiramycin extension modules) or a 14-membered macrolide (erythromycin extension modules) that incorporates a propionate starter unit. One would have been motivated to produce such hybrid PKS enzymes because of the great therapeutic potential of novel polyketides that can be easily produced, in combinatorial fashion, using the system of

mixing and matching described by Khosla *et al.* One would have had a reasonable expectation of success that such combination of genes, modules, domains, and portions thereof would render functional polyketides due to the extensive similarities among modular PKS enzymes (see Khosla *et al.*).

Summary of Pending Issues

24. The following is a summary of the issues pending in the instant application; each issue must be addressed in a complete response to the instant Office action:

a) Claims 65, 66, and 68 stand objected to for improperly referring to an antecedent in the previous claim.
b) Claim 56 stands rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for the phrase "natural extension module".
c) Claim 57 stands rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for the phrase "produced by mutation".
d) Claims 70 and 71 stand rejected under 35 U.S.C. § 112, first paragraph, new matter.
e) Claim 73 stands rejected under 35 U.S.C. § 112, first paragraph, written description, for not having adequate written description for the loading module of monensin.
f) Claims 54-57, 59 and 63 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Kuhstoss *et al.*
g) Claim 58 stands rejected under 35 U.S.C. § 103(a) as being unpatentable over Kuhstoss *et al.*
h) Claims 73 and 75 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Khosla *et al.* (USPN 5,712,146).
i) Claims 60-62 stand objected to for depending from rejected claims.

Examiner's Comments

25. To simply the allowed claim, the Examiner suggests the following language which removes inherently functions and unneeded limitations:

---64. A type I polyketide synthase which produces a polyketide and which comprises a loading module and a plurality of extension modules, wherein said loading module is of the form (KSq)-(AT)-(ACP), wherein:

i) KSq is a ketosynthase domain that differs from an extension module KS domain by having a glutamine residue in place of the cysteine reside in the active site;
ii) AT is an acyltransferase domain selected from the group consisting of:
AT of module 6 of the niddamycin PKS,
AT of module 4 of the FK506 PKS, and
AT5 of the spiramycin PKS; and
iii) ACP is an acyl carrier protein.---

26. Considering Claim 70, the Examiner notes that particular combinations of hybrid PKSs cannot be rendered obvious by Khosla *et al.* (USPN 5,712,146) despite its broad disclosure of mixing and matching modules and domains of PKSs because the combinations (i.e., two particular domains or modules together) cannot be rendered obvious. Moreover, Claims 60-62, 64-66 and 68 require particular combinations being obvious because particularly KSq-loading domains must be combined with noted extender AT domains. Thus, for Khosla *et al.* to render obvious Claims 60-62, 64-66 and 68, particularly the combination of a tylosin KSq and a spiramycin AT5 would have to be rendered obvious; and it is not.

Conclusion

27. Claims 54-59, 63, 70, 71, 73, and 75 are rejected. Claims 65, 66, and 68 stand objected to; Claims 60-62 stand objected to as well but would be allowable if rewritten in independent form. Claim 64 is allowed. The instant Office action is non-final.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kathleen M. Kerr whose telephone number is (571) 272-0931. The examiner can normally be reached on Monday through Friday, from 9:00am to 6pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathupura Achutamurthy can be reached on (571) 272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Kathleen M Kerr
Primary Examiner
Art Unit 1652

June 10, 2005